

Operations on the Colon

The Role of Antibiotics in Preoperative Preparation

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■ *A study was carried out on 183 patients in an attempt to evaluate the role of antibiotics in the preoperative preparation of the colon.*

Kanamycin, neomycin and a placebo were administered in a double-blind fashion during a 72-hour period preceding operation. In addition, mechanical cleansing of the bowel was done in all cases.

Considering only the criteria of mortality and the incidence of postoperative wound and peritoneal infections in this preliminary report there was no apparent significant difference between patients receiving antibiotics and those receiving a placebo.

INTESTINAL "sterilization" has been common practice for more than two decades, but there are still many unresolved questions about preoperative preparation of the colon. The purpose of using chemotherapeutic agents and antibiotics before operations on the rectum and colon is to reduce the risk of postoperative infection. Many investigators attribute the improved morbidity and mortality rates in recent years largely to this practice, although not overlooking the contribution of improved anesthesia and other refinements in preoperative and postoperative management.

In some animal studies, antimicrobial drugs have also been shown to favor the healing at the site of intestinal anastomosis and to increase survival when segments of bowel are devascularized.^{3,8} It is extremely difficult, however, to evaluate these potential advantages in clinical situations.

On the other hand the potential disadvantages or risks of antimicrobial therapy have recently re-

ceived increased attention.^{9,11} Foremost is the possibility of developing drug-resistant strains of bacteria and superinfections. This risk may vary, depending upon the predominant strains in the environment. Staphylococcal enterocolitis is a serious complication related to the suppression of the normal bacterial flora in the intestinal tract. Although commonly associated with such broad spectrum antibiotics as the tetracyclines, this complication may also occur following the use of oral neomycin and kanamycin, two of the agents commonly used in preoperative preparation today.⁴

Recently it was suggested that the "sterilized" bowel may be more vulnerable to the growth of recurrent tumor at the suture line. Vink¹⁰ and Cohn² in studies of Brown-Pearce tumors in rabbits, showed that use of intestinal antibiotics was associated with an increase in the rate of metastasis as well as the incidence of recurrence at the site of anastomosis in the colon. However, there is as yet no indication of similar effect in humans.

In an attempt to clarify some of these problems a study was carried out to evaluate the preoperative use of antibiotics as compared with only mechanical cleansing of the colon.

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Method

The study was in two phases. In Phase I, five groups of 20 patients each were given two different dosage regimens of kanamycin and of neomycin and a placebo. Capsules identical in appearance were prepared, containing variously 350 mg of neomycin base, 500 mg of neomycin base, 350 mg of kanamycin base, 500 mg of kanamycin base, or a placebo.* (The base equivalent of 500 mg of the sulfate of either drug is 350 mg base.) Drugs were dispensed to each patient in a double-blind fashion. An envelope system set up from a random numbers table was used to insure random administration.

The antibiotic or placebo was started 72 hours before operation on the following schedule: two capsules every hour for four hours, followed by two capsules every six hours until midnight of the day before operation.

The code for these five groups was not broken until the clinical and bacteriological evaluations had been completed on all patients.

In Phase II, four groups of 25 patients were given drugs which were coded as A, B, C or D. Two of the drug groups consisted of 500 mg of kanamycin sulfate and two groups consisted of placebo in identical capsules. To assure the capsules were given at random, the same code system used in Phase I was followed. Two capsules of each preparation were given every hour for four hours, starting 72 hours before operation. This was followed by three capsules every six hours until the midnight before operation. No other preoperative antibiotic therapy was given unless specifically indicated (for pulmonary or urinary tract infection or the like). Two patients in Group A, one in Group C, and one patient in Group D received other antibiotics during the week preceding operation. One additional patient in Group C received sulfasoxazole (Gantrisin®) during this period. During the postoperative period, antibiotics were administered only when specifically indicated by the occurrence of some infection. The cases were evenly distributed among the four groups in which a possibility existed that preoperative or postoperative antibiotics might have predisposed to the occurrence of wound or peritoneal infection.

In addition to the coded drugs, all patients in

*Bristol Laboratories prepared and supplied the capsules with a sealed code.

Phase I and Phase II received the following regimen for mechanical cleansing of the bowel:

- A low residue diet was started three days before operation.
- A liquid diet was given on the day before operation.
- 60 ml of castor oil was administered (except to patients with ulcerative colitis) with the first dose of the drug and repeated at noon on the day before operation.
- The majority of the patients (but not those with ulcerative colitis) received tap water enemas during the afternoon or evening of the day preceding operation.

In the Phase II study, five patients were excluded because, for one reason or another, the intended operation was not carried out. Four additional patients were excluded because clinical follow-up and bacteriological analysis were not completed. By coincidence, each of the four groups had one of these patients. Consequently, the code for this phase has not been broken to insure an unbiased analysis of the final results.

Patient Selection

Any patient with a known or suspected lesion of the colon or rectum was admitted to the study if the proposed operation could be delayed for the three days required for the preoperative regimen. Patients with any significant degree of intestinal obstruction were excluded. Also excluded were patients in whom colostomy was contemplated in advance, lest including them should introduce a large number of cases in which the colon was incised within the peritoneal cavity.

The age distribution of the four groups in Phase II is shown in Table 1. It was comparable with the age incidence in Phase I. Detailed clinical data on Phase I patients have been previously reported by Gaylor, Clarke, Kudinoff and Finegold.⁵

Among indications for operation, malignant disease was predominant. The kinds of cases were spread uniformly in all four groups except for a relatively high proportion of benign lesions in Group B.

The types of operative procedures performed also were fairly evenly distributed among the four groups. Most of the operations were performed by members of the senior resident staff. An "open technique" was used for colon resection and anastomosis. The total of 91 operations included only one colostomy, carried out in a Group D

TABLE 1.—*Age of Patients in Four Groups (Phase II Study)*

Drug Group	Per Cent of Group	
	Over 50 Years	Over 70 Years
A.....	92%	17%
B.....	78	22
C.....	91	39
D.....	86	43

patient as a palliative procedure. Palliative resections carried out in patients with far advanced carcinoma were also evenly distributed among the groups. Each group also included several patients in whom peritoneal contamination was already present at the time of operation. In four patients, the colon was not opened at the time of operation. In one of these patients, disseminated adenocarcinoma was encountered and the procedure was limited to a biopsy. In the other three patients there was primary disease of adjacent organs in which involvement of the colon could not be excluded preoperatively.

Results

Side Effects. The incidence of side effects such as nausea, vomiting, abdominal pain or diarrhea was negligible. In no instance was it necessary to discontinue the drug for these reasons. There were also no significant differences apparent between the various agents and dosages used in Phase I and Phase II.

Condition of the Bowel. The mechanical cleansing of the bowel by the regimen used in this study was considered satisfactory in all cases.

Postoperative Infections. The postoperative infections encountered in the Phase I study are shown in Table 2. Although the number of patients in each group is small, it is interesting that the lowest incidence of postoperative infections related to the surgical procedure occurred in the patients receiving a placebo. Staphylococcal enterocolitis developed postoperatively in four patients, all of whom had received antibiotics before operation.

Wound and peritoneal infections encountered in the Phase II study are shown in Table 3. Although it has not been determined which groups received antibiotics or placebo, it can be seen that no possible combination of any two of the four groups would show a statistically significant difference.

Mortality. The deaths occurring in the two studies are shown in Tables 4 and 5. If one postulated that the patients in Groups A and C received the same agent, then the ratio of deaths due to infection in the placebo versus kanamycin group could be four to two (or two to four). Considering the number of patients in the study, this difference is not statistically significant. On the other hand, if the patients in Groups A and B or Groups A and D received the same agent, then the number of deaths resulting from infections would be equal in the placebo and antibiotic groups. In the Phase II Group, three additional deaths occurred which were not related to infection: One patient with cirrhosis of the liver died of massive hemorrhage from esophageal varices; another died of multiple pulmonary emboli, and the third of metastatic disease. Seven of the eight deaths occurred in patients with malignant disease. Three of these patients had distant metastatic lesions at the time of death.

Discussion

In the numerous reports which have appeared in the literature concerning the effectiveness of antibiotics and chemotherapeutic agents in reducing postoperative morbidity and mortality associated with operations on the rectum and colon, the conclusions have rarely been supported by well controlled studies comparing treated and untreated patients. The present study was carried out in a way to minimize bias in the analysis of the results.

Although each of the five drug groups in the Phase I Study was relatively small in size, it is interesting to note that the incidence of infections

TABLE 2.—*Incidence of Infections Related to Operation (Phase I Study)*

Drug	Each Capsule*	Number of Operations	Wound Infections	Perineal Infections	Peritoneal Infections	Enterocolitis
Neomycin 500 mg.....		18	4	2	0	1
Kanamycin 500 mg.....		20	7	2	0	1
Neomycin 350 mg.....		18	2	3	2	2
Kanamycin 350 mg.....		19	7	3	0	0
Placebo		17	2	0	2	0

*Dosage was begun 72 hours before operation on schedule of two capsules every hour for four hours, then two capsules every six hours until the midnight before operation.

TABLE 3.—Incidence of Peritoneal and Wound Infections by Group* (Phase II Study)

Group	No. Treated	Total Infections	Peritoneal Infections	Wound Infections
A.....	24	9	2	7†
B.....	23	7	2	5†
C.....	23	6	2	4
D.....	21	8	3	5

*Grouped according to four different coded preoperative preparations.

†Infection limited to drain site in one patient in each of these two groups.

TABLE 4.—Death in Each Drug Group (Phase I Study)

Drug	Each Capsule†	Total Patients	Total Deaths	Deaths Related to Infection
Neomycin 500 mg.....	20	20	1	1*
Kanamycin 500 mg.....	20	20	0	0
Neomycin 350 mg.....	20	20	2	1
Kanamycin 350 mg.....	19	19	2	0
Placebo	19	19	5	2†

*Infected before operation.

†One of these patients had a "pull-through" operation with probable impairment of blood supply; second patient had perforation of colon due to carcinoma and was infected prior to operation.

‡Dosage was begun 72 hours before operation on schedule of two capsules every hour for four hours, then two capsules every six hours until the midnight before operation.

TABLE 5.—Deaths in Each Group* (Phase II Study)

Group	Total Patients	Total Deaths	Deaths due to Infection
A.....	24	2	1
B.....	23	3	2
C.....	23	1	1
D.....	21	3	2
Total.....	91	9	6

*Grouped according to four different coded preoperative preparations.

related to operation was the lowest in the group receiving the placebo. In this placebo group, *Staphylococcus aureus* was never recovered from cultures of stool or of exudate from infections related to operation. No discernible differences in effectiveness were found between the two antibiotics or between the two dosage regimens employed.

Although the code has not yet been broken in the Phase II Study, some pertinent observations can be made. Considering only the criteria of mor-

tality and the incidence of postoperative wound and peritoneal infections, there is no apparent significant difference between patients receiving kanamycin and those receiving a placebo. However, this is only a preliminary report and it does not include an analysis of other infections occurring in this group such as pneumonitis and urinary tract infections. Subsequent analysis and correlation of bacteriological data will be reported later.

The advisability of the routine use of antibiotics in preoperative preparation of the colon has previously been questioned by Tyson and Spaulding as well as by other investigators.^{6,7,9} Although no definite conclusions can be reached in the present study as yet, our experience also raises doubt as to the necessity or desirability of routine preoperative "sterilization" of the bowel.

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